Development and validation of a motorized focused ultrasound system for the controlled delivery of large molecules to the rodent brain under 7T MRI guidance

Remi Magnin, Sébastien Mériaux, Denis Le Bihan, Erik Dumont, Benoît Larrat

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R. Magnin[*1,2], S. Mériaux[1], D. Le Bihan[1], E. Dumont[2], B. Larrat[1]

[1]UNIRS, CEA/DSV/I2BM/Neurospin, Gif sur Yvette, France.
[2]Image Guided Therapy, Pessac, France.
[*]remi.magnin@cea.fr

***Abstract* —The use of focused ultrasound combined with microbubbles has shown the capability to increase the permeability of the Blood Brain Barrier (BBB) locally, transiently and non-invasively, allowing the delivery of large molecules to the brain. Magnetic Resonance Imaging is of great interest to precisely monitor the disruption. In this study, we have shown the possibility to use our motorized system to open the BBB along arbitrary trajectories under 7T MRI guidance and to test different acoustic conditions on a single animal.**

***Index terms* - Contrast agents, Magnetic Resonance Imaging, Ultrasound**

I. INTRODUCTION

The BBB controls the exchanges between blood and the Central Nervous System (CNS), preventing the access of large molecules to the brain, including promising drugs.

Short transcranial sonications of circulating microbubbles have shown its capability to increase the permeability of the BBB locally, transiently, and non-invasively, allowing drug delivery to the brain [1].

MRI monitoring of the technique allows choosing precisely the disruption site as well as controlling the deposited acoustic intensity prior to the opening by the use of Magnetic Resonance acoustic Radiation Force Imaging (MR-ARFI)[2], but also the visualization and the quantification of the phenomenon *via* the injection of MR Contrast Agents (MR-CA).

In order to be able to target specific locations of the brain, we developed a MR compatible motorized system, allowing the displacement of the ultrasound transducer inside a preclinic high field MRI.

In this study, we demonstrate the possibility to use this system to increase the permeability of the BBB along arbitrary trajectories, and also the capability to test different acoustic conditions on the same animal during one single session.

II. MATERIALS AND METHODS

II.1. Animal preparation and BBB opening

After head shaving, Sprague Dawley rats (n=5) were maintained under isoflurane anesthesia in stereotactic position inside a 7T preclinical scanner (Pharmascan, Bruker). A single channel spherically focused transducer (1.5 MHz, F/D=0.8, F= 20 mm) was coupled to the head with a water balloon and echographic gel. A catheter was inserted in the caudal vein. 200 μL of Sonovue (Bracco) are injected in the catheter, immediately followed by the sonications (see II.3). 200 μL of Gadolinium (Gd) chelates (Guerbet) are then injected through the catheter.

II.2. MRI acquisitions and BBB disruption location

Prior to the ultrasound session, T_1-weighted and T_1-mapping reference scans were acquired. Anatomy T_2-weighted scan was also acquired and sent in real time to the ultrasound console to choose the sonication location. MR-ARFI were then performed and sent to the ultrasound console to record the current focal spot position, and a retrocontrol allowed the precise positioning of this focal spot with respect to the chosen location. After BBB opening, T_1-weighted scan was performed to visualize the contrast enhancement at the sonoporated regions, while a T_1-mapping allowed, after post-processing, calculating the Gd concentration everywhere in the brain.

II.3. Ultrasound sessions

For the first experiment, different mechanical trajectories were programmed (letters) for the BBB disruption with continuous sonications and constant displacement speed (10 mm/s).
In a second experiment, we tested the influence of the acoustic pressures on two animals by defining a square with different acoustic intensities on each of its edges (0.16, 0.32, 0.49, 0.65 MPa peak negative pressures as calibrated with an hydrophone in a degassed water tank and 0.65, 0.97, 1.3, 1.6 MPa).

III. RESULTS

Due to T_1 shortening effect induced by the presence of Gd chelate, a contrast enhancement is visible at the expected locations compared to the rest of the brain (Figure 1), confirming that the BBB has been opened along the planned trajectory.

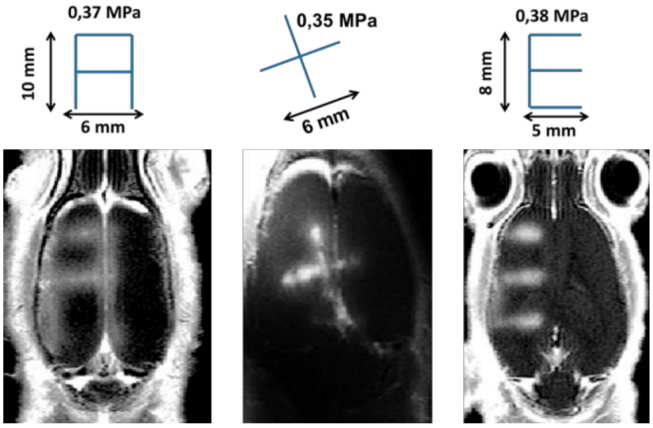

Figure 1: T_1 weighted images acquired after BBB opening along different mechanical trajectories and GD chelates injection. A scheme of the performed trajectory is presented above each image.

No Gd chelate penetration was observed for acoustic pressures below the disruption threshold, estimated to be around 0.3 MPa [3] (Figure 2). The acquisition of a T_1 map then enables to quantify drug uptake in brain tissue. Above 0.5 MPa at focus, no significant difference was found in the maximum Gd concentration that was measured although the width of the disrupted line was increased as expected.

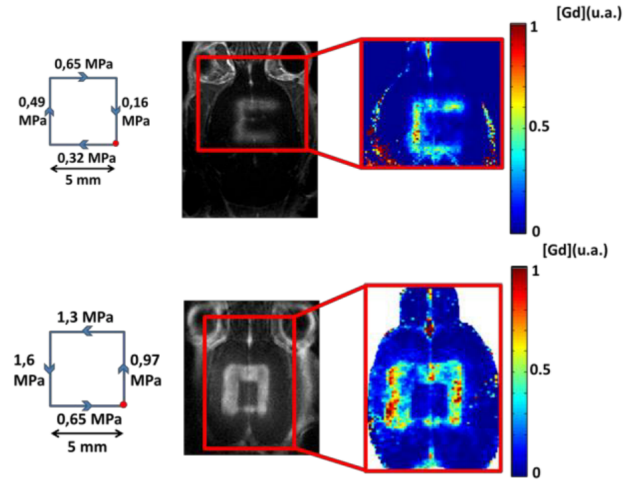

Figure 2: Acoustic pressure influence on two animals. From left to right: a scheme of the performed sonication, the T_1-weighted image acquired after Gd injection, and the corresponding Gd concentration map (in arbitrary unit).

IV. DISCUSSION – CONCLUSION

This study demonstrates that this new MR guided motorized device can be used to deliver drugs to different arbitrarily chosen regions in the rodent brain after a unique systemic injection. The real time image reconstruction coupled to a retrocontrol of the motors allows choosing the desired region to be opened on an anatomy image. The delivered concentration can be tuned by adjusting the acoustic pressure, and measured using quantitative MRI sequences.

The motors offer the capability to choose between a focal disruption or a wider permeabilization of the BBB depending on the applications. However, the safe parameters for large opening have to be further investigated as all previous studies were performed on focal opening.

Our setup also offers the unique possibility to test on the same animal different acoustic conditions (pressure, shot duration, duty cycle) while ensuring same anesthesia and temperature levels. The influence of physiological parameters such as vascular density on BBB opening efficiency can also be assessed. It may result in a significant reduction of the number of animals and the acquisition time required for drug delivery experiments, and may also offer a real gain of reproducibility by planning precisely the disruption location.

ACKNOWLEDGEMENTS

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